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P032789GB

28DEC02 E773710-4 D00019
P01/7700 0.00-0230162.0

2. Patent application number
(The Patent Office will fill in this part)

0230162.0

24 DEC 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Metris Therapeutics Limited
515 Eskdale Road
Winnersh
Wokingham
RG41 5TU

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

GB

07729320002

4. Title of the invention

Compounds useful in inhibiting angiogenesis

5. Name of your agent *(if you have one)*

Carpmaels & Ransford

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

43 Bloomsbury Square
London
WC1A 2RA

Patents ADP number *(if you know it)*

83001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body

Yes

See note (d))

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Continuation sheets of this form	0
Description	45
Claim(s)	3
Abstract	0
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Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	0
Request for preliminary examination and search *(Patents Form 9/77)*	0
Request for substantive examination *(Patents Form 10/77)*	0
Any other documents *(please specify)*	0

11. I/We request the grant of a patent on the basis of this application.

Signature: Carpmaels & Ransford
Carpmaels & Ransford

Date: **24th December 2002**

12. Name and daytime telephone number of person to contact in the United Kingdom: **H. R. Goodfellow** **020-7242 8692**

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Compounds useful in inhibiting angiogenesis

Technical Field

This invention relates to compounds that are useful in treating vascular endothelial growth factor (VEGF)-mediated disorders. In particular, this invention relates to compounds useful in treating endometriosis. The invention also relates to the use of these compounds and to pharmaceutical compositions comprising these compounds.

Technical Background

Vasculogenesis and angiogenesis play important roles in a variety of physiological processes such as embryonic development, wound healing, organ regeneration and female reproductive processes. Unregulated angiogenesis occurs in a number of disease states. These include benign conditions such as endometriosis but also life-threatening conditions such as malignant tumours. The diverse disease states in which unregulated angiogenesis is present have been grouped together as angiogenic dependent or angiogenic associated diseases (Klagsburn & Soker, 1993, Current Biology 3(10):699-702; Folkman, 1991, J. Natl., Cancer Inst. 82:4-6; Weidner, et al., 1991, New Engl. J. Med. 324:1-5. Folkman & Shing, 1992, J. Biological Chem. 267(16):10931-34).

Several polypeptides with in vitro endothelial cell growth promoting activity have been identified but VEGF has been reported to be an endothelial cell specific mitogen (Ferrara & Henzel, 1989, Biochem. Biophys. Res. Comm. 161:851-858; Vaisman et al., 1990, J. Biol. Chem. 265:19461-19566).

VEGF is a family of dimeric glycoproteins that belong to the platelet derived growth factor (PDGF) superfamily of growth factors. In addition to VEGF-A, VEGF-B, VEGF-C and VEGF-D there is the so-called placental growth factor (PlGF). Some of the genes for these growth factors can be expressed as different isoforms. For example the VEGF-A gene is differentially spliced into a number of isoforms the most common messenger RNA's encoding polypeptides of 121, 165 and 189 amino acids. The compounds

described in this invention are likely to have inhibitory activity against the VEGF family and possibly against other related families to a greater or lesser extent.

Thus the ability to inhibit the activity of VEGF and its stimulation of new blood vessel formation represents a selective pharmaceutical approach for a number of clinical conditions.

As mentioned above, one disease in which VEGF plays a role is endometriosis. Endometriosis is the name given to the disease resulting from the presence of endometrial cells outside of the uterine cavity. This disease affects women during their childbearing years with deleterious social, sexual and reproductive consequences. Endometriosis has been proposed as one of the most commonly-encountered diseases of gynaecology, with the incidence of endometriosis in the general population being estimated to be around 5%, although it is thought that at least 25% of women in their thirties and forties may have endometrical legions from this disease.

The development and maintenance of endometriosis involves the establishment and subsequent sustained growth of endometrial cells at ectopic sites, most commonly the pelvic peritoneum and ovaries, following retrograde menstruation (see Thomas & Prentice (1992) Repro. Med. Rev. (1): 21-36). Implantation of autologous non-malignant ectopic tissue is a unique phenomenon suggesting that an abnormal host response may be present in women who develop this disease. This theory is supported by the fact that only a minority of women will develop the disease in spite of the common occurrence of retrograde menstruation as a source of endometrial tissue.

There are many theories proposed for the origin of endometriosis and various cellular and biochemical constituents of the peritoneal fluid have been reported to play an important role in the pathogenesis of this disease. Alterations in multiple aspects of both humoral immunity and cell-mediated immunity have also been reported in suffering individuals.

The heritable aspects of endometriosis have been investigated in several studies (Moen & Magnus (1993) Acta Obstet. Gynecol. Scand., 72: 560-564; Kennedy *et al*, (1995) J.

Assist. Repro. Gen., 12(1): 32-35; Malinak *et al* (1986) Am. J. Obstet. Gynecol., 137(3): 332-337; Treloar *et al.*, (1999) Fertility Sterility 71(4) 701-710). On the basis of these studies, it has been hypothesised that endometriosis has in part a genetic basis. However, the precise aetiology of this disease still remains unknown.

The growth and development of endometrial tissue appears to depend on the presence of oestrogen. Drugs have thus been developed that reduce the body's oestrogen content in order to reduce the growth of endometrial implants at ectopic sites. Strategies include mimicking pregnancy, preventing ovulation using contraceptive agents, blocking the action of progesterone and mimicking the menopause. Although some of these drugs have proved successful, many cause unpleasant side-effects including post-menopausal like side effects and infertility, which mean that treatment must be discontinued to avoid the side-effects becoming permanent. Furthermore, all drugs described to date act by relieving the symptoms of the disease and are not in any sense curative. This makes a patient permanently dependent on the drug if the symptoms of disease are to be kept at bay.

Presently, the only treatment of endometriosis that is effective in the long term involves surgery. Therefore, there remains a great need for the discovery of agents with effective prophylactic, therapeutic and diagnostic value against endometriosis.

VEGF, also known as vascular permeability factor is secreted by tumours (Dvorak, H. et al., (1979) J. Immunol., 122, 166-174; it is a multi-functional cytokine that promotes the formation of blood vessels (angiogenesis). The growth of most tumours is dependent on the development of an adequate blood supply and therefore the prevention of angiogenesis by the inhibition of VEGF provides a potential strategy for the development of anti-cancer pharmaceuticals.

The expression of VEGF correlates with poor prognosis (Tabone, M. D. et al., (2001) Clin. Cancer Res., 7, 538-543) and has been detected in renal cell carcinoma (Slaton, J. W. et al., (2001) Am. J. Path., 158, 735-743), mammary carcinoma (Adams, J. et al., (2000) Cancer Res., 60, 2898-2905), head and neck squamous cell carcinoma (Minet, H. et al., (2000) Br. J. Cancer, 83, 775-781), bladder cancer (Inoue, K. et al., (2000) Clin. Cancer Res., 6, 4866-

4873), oesophageal carcinoma (Shih, C. H. et al., (2000) Clin. Cancer Res., 6, 1161-1168),osteosarcoma (Kaya, M. et al., (2000) Clin. Cancer Res., 6,572-577), colonic carcinoma (Cascinu, S. et al., (2000) Clin. Cancer Res., 6, 2803-2807), ovarian carcinoma (Shen, G. H. et al., (2000) Br. J. Cancer, 83, 196-203), carcinoma of the cervix (Loncaster, J. A. et al., (2000) Br. J. Cancer, 83, 620-625), soft tissue sarcomas (Yudoh, K. et al., (2001) Br. J. Cancer, 84, 1610-1615), astrocytoma (Abdulrauf, S. I. et al., (1998) J. Neurosurg., 88, 513-520) and prostate carcinoma (Borre, M. et al., (2000) Clin. Cancer Res., 6, 1882-1890). Inhibition of VEGF and thereby reducing the ability of the tumour to become vascularized, either alone or in combination with other treatments such as chemotherapy or radiotherapy my therefore have clinical utility in these and other human and animal tumours.

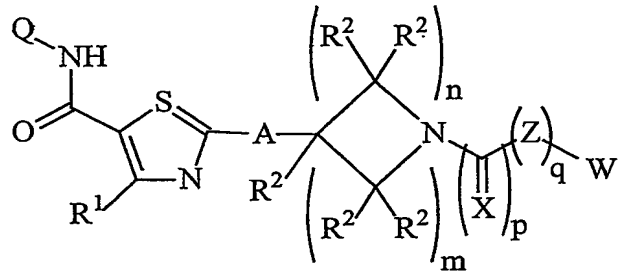
A number of non-oncological clinical indications involve abnormally increased angiogenesis and the inventions described herein may be the basis for therapeutic intervention. Macular degeneration and retinopathy can occur as a result of the ageing process or occur as a result of other diseases in particular diabetes. High levels of VEGF have been implicated in these conditions (Funatsu, H. et al., (2002) J. Cataract Refract. Surg. 28, 1355; Noma, H. et al., (2002) Arch. Ophthalmol. 120, 1075-80). It has been suggested that inhibition of VEGF may be useful (Aiello, L.P. (1997) Ophthalmic Res., 29,354-62) and in particular may prevent the oedema that occurs at the early stages of diabetic retinopathy (Lu, M. et al., (2002) Ophthalmol. Clin. North Am., 15, 69-79). Diabetic nephropathy and neuropathy may have a common biochemical dysfunction to retinopathy (Tilton, R.G. (2002) Microsc. Res. Tech., 57, 390-407) and an anti-VEGF pharmaceutical approach may be appropriate.

Inhibition of VEGF may also be a suitable therapeutic strategy in atheroma (Blann, A.D., (2002) Clin. Sci. 102, 187-94) and in rheumatoid arthritis (Afuwape, A.O., (2002) Histol. Histopathol., 17, 961-72) and psoriasis (Creamer, D. et al., (2002) Arch. Dermatol., 138, 791-6); VEGF has been implicated in the pathogenesis of both conditions.

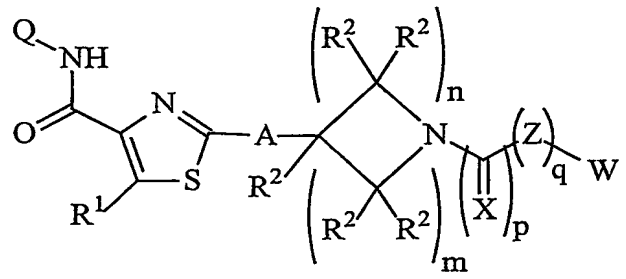
It is an object of the present invention to provide compounds that are useful in treating VEGF-related disorders.

Summary of the Invention

According to a first embodiment of the present invention there is provided a compound of formula (I) or formula (II):



(I)



(II)

wherein:

Q is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, amino, alkylamino, dialkylamino, carboxyl, carboxylalkyl, esterified carboxyl, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy, or heterocyclic group;

A is a single bond or alkylene;

X is O or S;

Z is O, S or NR^3;

p is 0 or 1

q is 0 or 1;

n is an integer from 0 to 10;

m is an integer from 0 to 10;

W is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, amino, alkylamino, dialkylamino, carboxyl, carboxylalkyl, esterified carboxyl, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy, or heterocyclic group;

R^1 is H or alkyl;

R^2 is independently H or alkyl; and

R^3 is H or alkyl;

or a pharmaceutically acceptable derivative thereof.

The term "pharmaceutically acceptable derivative" as used herein, means any pharmaceutically acceptable salt, addition compound, or any other compound which upon administration to a recipient is capable of providing, whether directly or indirectly, a compound of the invention or a pharmaceutically acceptable metabolite.

The term "pharmaceutically acceptable metabolite" as used herein, means a metabolite or residue of a compound of the invention which gives rise to a biological activity exhibited by the compounds of the invention.

The term "pharmaceutically acceptable salt", as used herein, refers to a salt prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic or organic acids and bases.

Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, sulfuric, and phosphoric acids. Appropriate organic acids may be selected, for example, from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic, stearic, sulfanilic, algenic, and galacturonic. Examples of such inorganic bases include metallic salts made from aluminium, calcium, lithium, magnesium, potassium, sodium, and zinc. Appropriate organic bases may be selected, for example, from N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumaine (N-methylglucamine), and procaine.

As used herein, the term "alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5, C_6 or C_7. Where acyclic, the alkyl group is preferably C_1 to C_{10}, more preferably C_1 to C_6, more preferably methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, isobutyl or tertiary-butyl) or pentyl (including n-pentyl and iso-pentyl), more preferably methyl. It will be appreciated therefore that the term "alkyl" as used herein includes alkyl (branched or unbranched), alkenyl (branched or unbranched), alkynyl (branched or unbranched), cycloalkyl, cycloalkenyl and cycloalkynyl.

As used herein, the term "lower alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical, wherein a cyclic lower alkyl group is C_5, C_6 or C_7, and wherein an acyclic lower alkyl group is C_1 to C_6, that is, methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl), more preferably methyl.

An alkyl group may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 or 2 substituents. Substituents may include halogen atoms and halomethyl groups such as CF_3 and CCl_3; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, amido, alkylamino, dialkylamino, cyano, azide, nitrato and nitro; sulphur containing groups such as thiol, alkylthiol, sulphonyl and sulphoxide; heterocyclic groups containing one or more, heteroatom, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl, carbolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl and pyrimidinyl; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl.

As used herein, the term "alkylene" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenylene or alkynylene) hydrocarbylene radical. Where cyclic, the alkylene group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5 to C_7. Where acyclic, the alkylene group is preferably C_1 to C_{16}, more preferably C_1 to C_4, more preferably methylene.

An alkylene group may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include halogen atoms and halomethyl groups such as CF_3 and CCl_3; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, amido, alkylamino, dialkylamino, cyano, azide, nitrato and nitro; sulphur containing groups such as thiol, alkylthiol, sulphonyl and sulphoxide; heterocyclic groups containing one or more, preferably one, heteroatom, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl.

As used herein, the term "aryl" means a cyclic or bicyclic aromatic group, such as phenyl or naphthyl.

As used herein, the term "heterocyclic" means a saturated or unsaturated cyclic or bicyclic group containing one or more heteroatoms, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl,

7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl, carbolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl and pyrimidinyl.

As used herein, the term "alkoxy" means alkyl-O-. As used herein, the term "lower alkoxy" means loweralkyl-O-. As used herein, the term "aryloxy" means aryl-O-.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine or chlorine radical.

Compounds of the invention of formula (II) are preferred.

Preferably, A is a single bond.

Preferably, X is O. Alternatively, it is preferred that X is S and Z is N.

Preferably, R^3 is H.

Preferably, p = 1.

Preferably, q = 0.

Preferably, the sum n +m is an integer from 2 to 10, more preferably 2 to 6, more preferably 2 to 4, more preferably 3 or 4, most preferably 4.

Preferably, n is from 0 to 3, preferably 2.

Preferably, m is from 0 to 3, preferably 2.

Preferably, n = 2 and m = 2.

Preferably, R^1 is H.

Preferably, each R^2 is H.

The substituents Q and W may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 or 2 substituents. Substituents may include halogen atoms and halomethyl groups such as CF_3 and CCl_3; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, amido, alkylamino, dialkylamino, cyano, azide, nitrato and nitro; sulphur containing groups such as thiol, alkylthiol, sulphonyl and sulphoxide; heterocyclic groups containing one or more, heteroatom, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl, carbolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl and pyrimidinyl; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl.

Preferably Q is a heterocyclic group, optionally substituted with 1, 2 or 3 substituents, preferably 2 substituents.

Preferably, Q is a phenyl group optionally substituted with 1, 2 or 3 substituents, preferably 2 substituents. Preferably Q is a phenyl group having at least one substituent selected from alkoxy, amide, carboxy, carboxylalkyl, alkoxy, cyano, halogen and a heterocyclic group.

Preferably Q is a phenyl group substituted with at least one group selected from methoxy, cyano, chlorine, fluorine, oxazolyl, tetrazolyl, oxazolyl substituted with lower alkyl, -

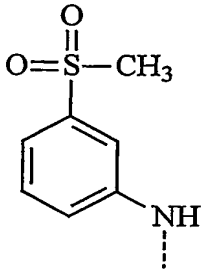
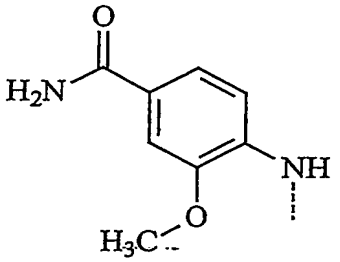
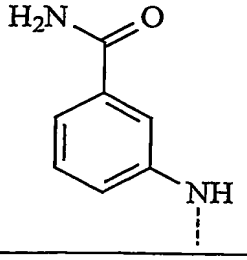
$C(O)NH_2$, $-C(O)NHR$, $-C(O)NR_2$, $-C(S)NH_2$ and $-NHC(O)R$, where R is lower alkyl, preferably methyl.

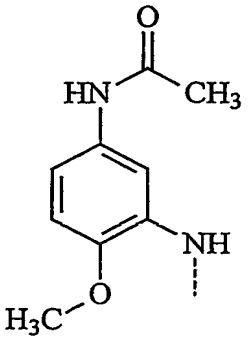
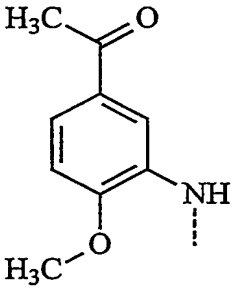
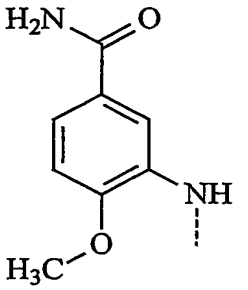
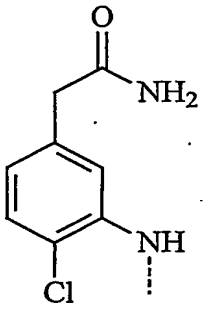
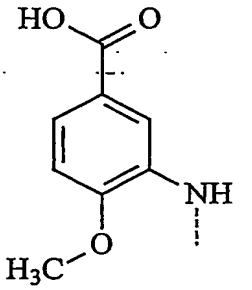
Q may be thiophenyl. Preferably, Q is thiophenyl substituted with a methoxy, cyano, chlorine, $-C(O)NH_2$, $-C(O)NHR$, $-C(O)NR_2$, $-C(S)NH_2$ or $-NHC(O)R$ group, where R is lower alkyl, preferably methyl.

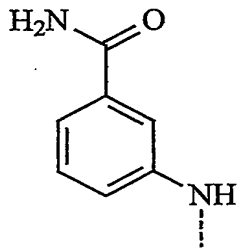
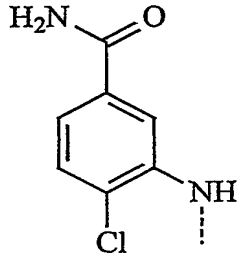
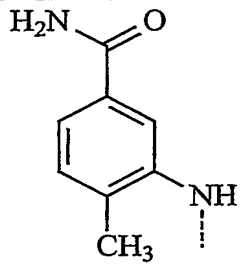
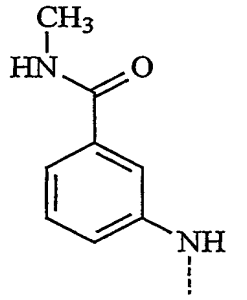
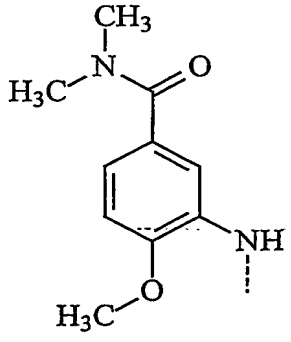
Q may be furanyl. Preferably, Q is furanyl substituted with a methoxy, cyano, chlorine, $-C(O)NH_2$, $-C(O)NHR$, $-C(O)NR_2$, $-C(S)NH_2$ or $-NHC(O)R$ group, where R is lower alkyl, preferably methyl.

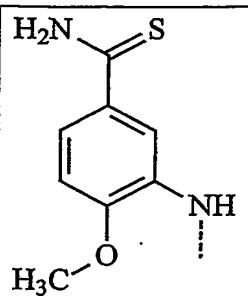
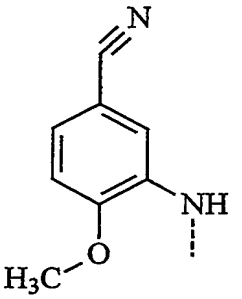
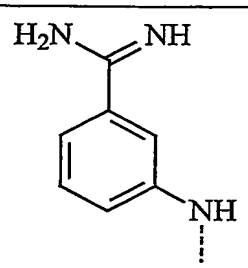
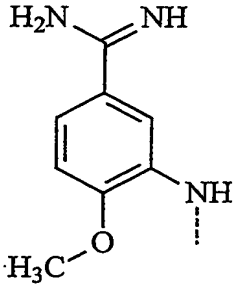
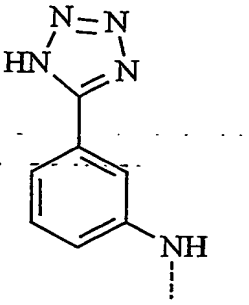
Preferably Q is a radical selected from the radicals set out in Table 1.

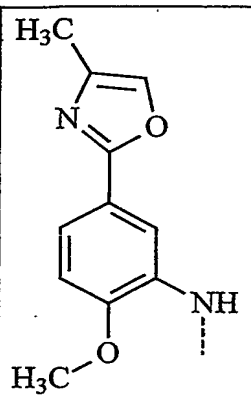
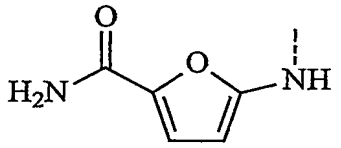
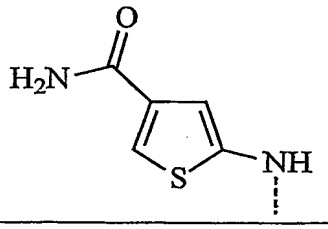
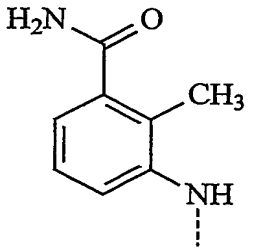
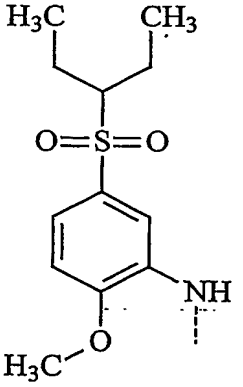
Table 1

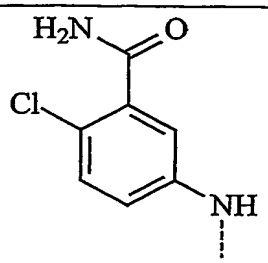
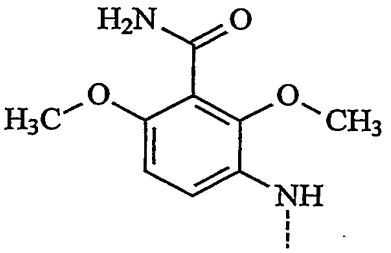
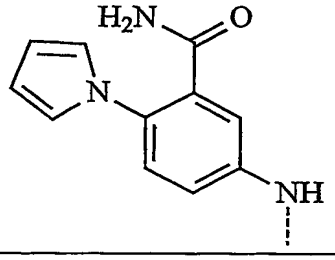
Q	**Radical**
Q^1	
Q^2	
Q^3	

Q^4	
Q^5	
Q^6	
Q^7	
Q^8	

Q^9	
Q^{10}	
Q^{11}	
Q^{12}	
Q^{13}	

Q^{14}	
Q^{15}	
Q^{16}	
Q^{17}	
Q^{18}	

Q^{19}	
Q^{20}	
Q^{21}	
Q^{22}	
Q^{23}	

Q^{24}	
Q^{25}	
Q^{26}	

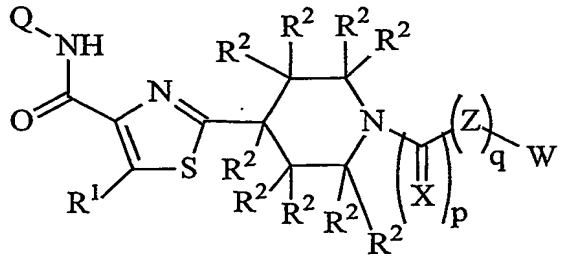
Preferably Q is 5-carbamoyl-2-methoxy-phenyl.

Preferably W is a heterocyclic group, optionally substituted with 1, 2 or 3 substituents, preferably 2 substituents. Preferably W is an optionally substituted phenyl, oxazolyl, diazolyl, quinolinyl, benzofuranyl or pyrindinyl. Preferably, the substituents are independently selected from alkoxy, amide, carboxy, carboxylalkyl, alkoxy, cyano, halogen and a heterocyclic group, more preferably, methoxy, cyano, chlorine, oxazolyl, tetrazolyl, oxazolyl substituted with lower alkyl, $-C(O)NH_2$, -C(O)NHR, $-C(O)NR_2$, $-C(S)NH_2$ and -NHC(O)R, where R is lower alkyl, preferably methyl.

Alternatively, W is an alkyl, alkylene, alkylyne, alkyoxy or amine, carboxylalkyl, optionally substituted with a heterocyclic group. Preferably, the heterocyclic group is substituted with 1, 2 or 3 substituents independently selected from alkoxy, amide, carboxy, carboxylalkyl, alkoxy, cyano, halogen and a heterocyclic group. More preferably the substituents are methoxy, cyano, chlorine, oxazolyl, tetrazolyl, oxazolyl substituted with

lower alkyl, -C(O)NH_2, -C(O)NHR, -C(O)NR_2, -C(S)NH_2 and -NHC(O)R, where R is lower alkyl, preferably methyl.

Preferably, the compound of the invention has the formula (III):



formula (III)

wherein Q, R^1, R^2, X, Z, W, p and q are as defined above.

In one embodiment of the invention, the compound of formula (I) is preferably:

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(4,7-dimethylpyrazolo[5,1-*c*][1,2,4]triazin-3-yl)carbonyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-(1-benzofuran-2-ylcarbonyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-(3-phenyl-2-propynoyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide;

2-(1-{[2-(allylsulfanyl)-3-pyridinyl]carbonyl}-4-piperidinyl)-*N*-[5-(aminocarbonyl)-2-methoxyphenyl]-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(2-chlorophenyl)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(3,4-dimethylphenoxy)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({[4-(dimethylamino)phenyl]amino}carbonothioyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide;

or

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide.

According to a further aspect of the present invention there is provided a compound of the present invention for use in a method of treatment of disease.

The compounds of the present invention may preferably be employed in the treatment of VEGF-mediated disorders such as endometriosis, various malignant and non-malignant tumours, psoriasis and other skin conditions, atheromatous disease, rheumatoid arthritis, macular degeneration and the complications of diabetes including retinopathy, nephropathy and neuropathy.

According to a further aspect of the present invention there is provided the use of a compound of the present invention for use in the manufacture of a medicament for treating a VEGF-mediated disorder, preferably endometriosis or malignant tumours.

According to a further aspect of the present invention there is provided a method of treating a disease mediated by VEGF, such as endometriosis, comprising administering to a patient in need of such treatment an effective dose of a compound of the present invention.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention in combination with a pharmaceutically acceptable excipient.

The agents described could be used alone or conjointly with treatments such as anti-hormone therapy, surgery, radiotherapy or chemotherapy.

Compounds of the present invention may be administered in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use including transmucosal and transdermal use, for example a cream, ointment, gel, aqueous or oil solution or suspension, salve, patch, plaster or as a component of a lubricant for a condom; for nasal use, for an example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example a finely divided powder or a liquid aerosol; for intra-ocular, sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oil solution or suspension, or incorporated in a biodegradable polymer. In general the above compositions may be prepared in a conventional manner using convention excipients, using standard techniques well known to those skilled in the art of pharmacy. The preferred modes of administration of the compound are oral or intravaginal. Oral administration is particularly preferred.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

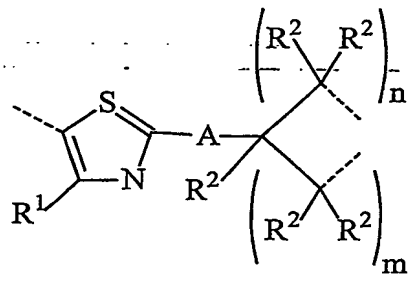
Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

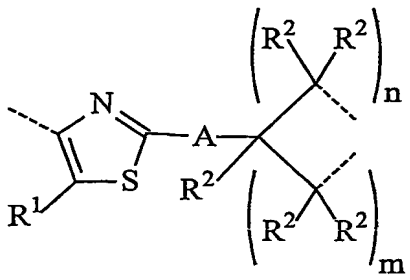
For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate. The compounds of the invention may also be provided in a biodegradable polymer, for example for use in conjunction with stents in surgery (e.g. adsorbed on a stent or applied directly to the site of the procedure for slow release of the active agent).

It will be appreciated that the dosage levels used may vary over quite a wide range depending upon the compound used, the severity of the symptoms exhibited by the patient and the patient's body weight. Without limitation to the present invention, typical dosages for treatment of endometriosis may be, for example, of the order of 1 microgram/kg/day to 1 milligram/kg/day, more preferably 10 microgram/kg/day to 0.25 milligram/kg/day orally. For intra-ocular administration, typical dosages would be of the order of 10 nanogram/kg/day to 1 microgram/kg/day. For treatment of tumours up to 5 milligrams/kg/day would be preferable. For intra-vaginal administration typical dosages would be 10 micrograms/kg/day to 0.25 milligrams/kg/day.

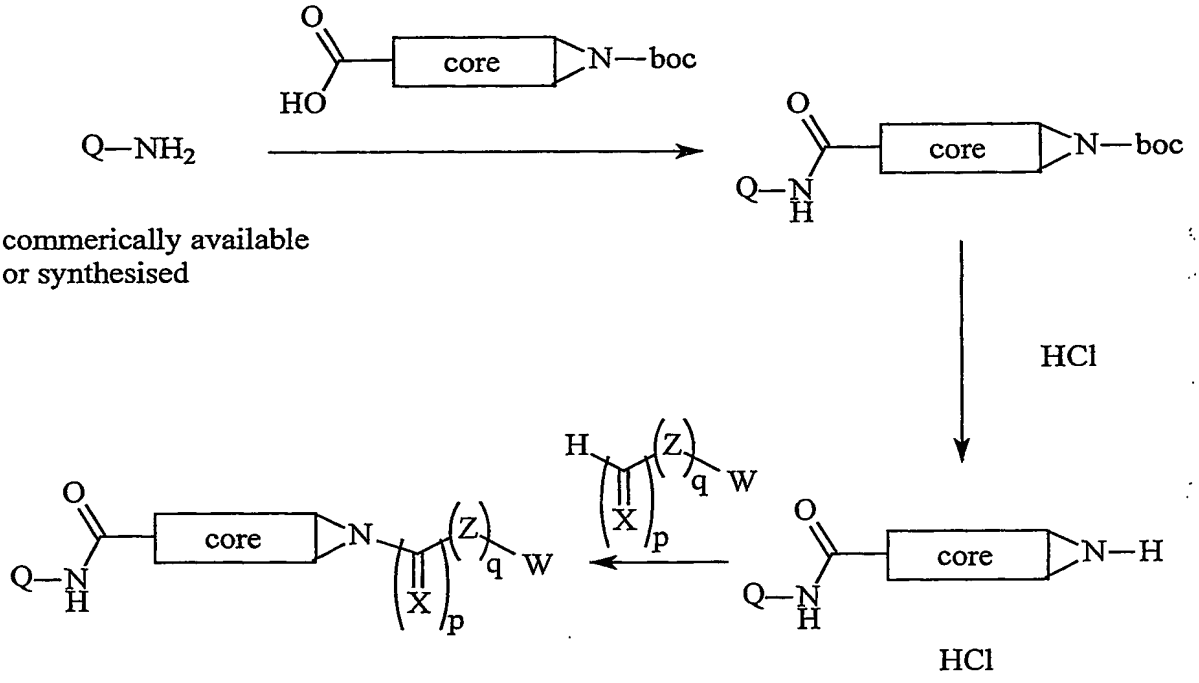
Compounds of this invention may be prepared by the general reaction scheme, Reaction Scheme 1, wherein by "core" is meant the radical



or



Reaction Scheme 1



The invention is now further illustrated by means of the following Examples.

Examples

Synthesis of Specific Compounds of the Invention

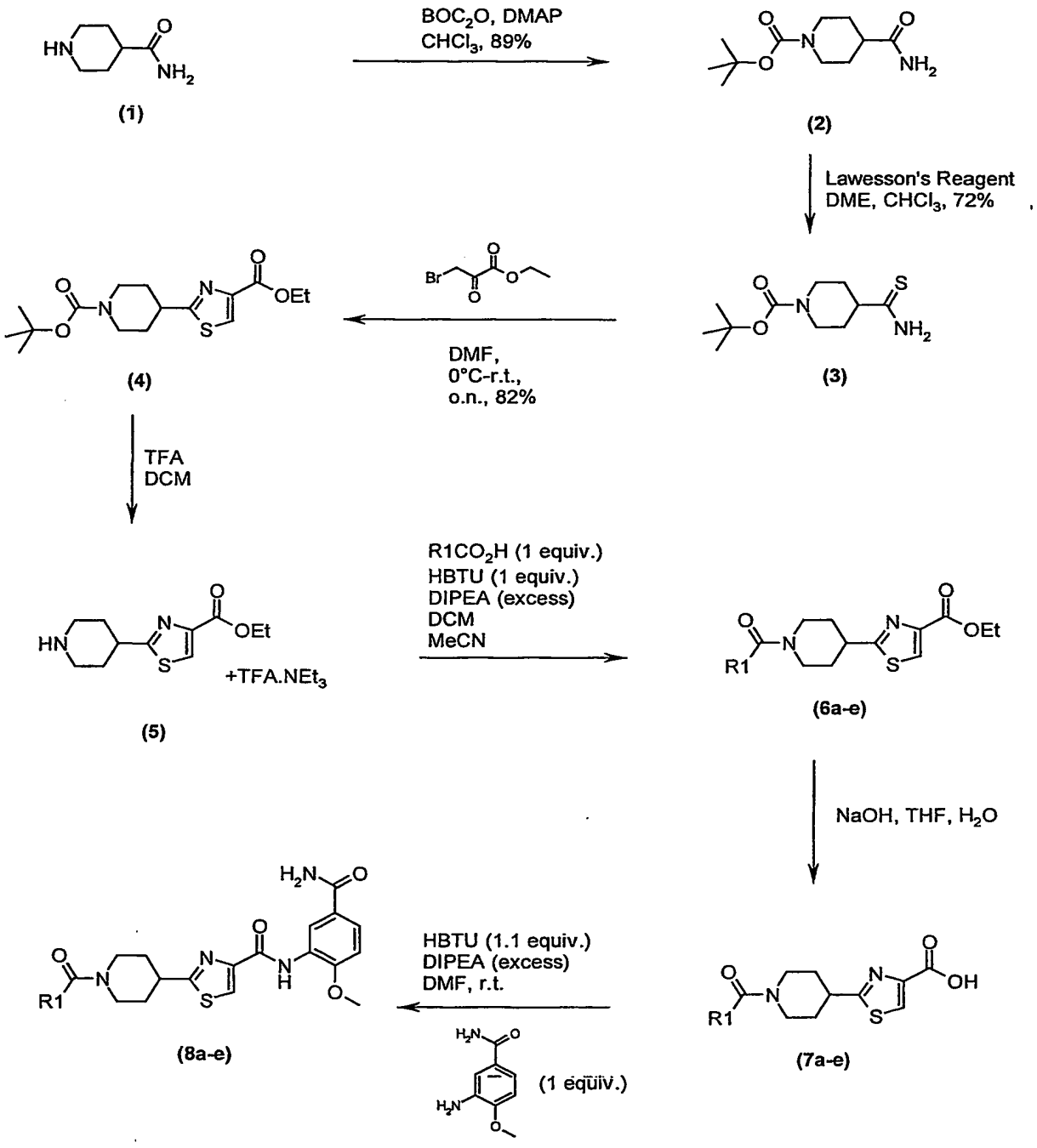
Examples 1-6

Preparation of *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(4,7-dimethylpyrazolo[5,1-*c*][1,2,4]triazin-3-yl)carbonyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide; *N*-[5-

(aminocarbonyl)-2-methoxyphenyl]-2-[1-(1-benzofuran-2-ylcarbonyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide; *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-(3-phenyl-2-propynoyl)-4-piperidinyl] -1,3-thiazole-4-carboxamide; 2-(1-{[2-(allylsulfanyl)-3-pyridinyl]carbonyl}-4-piperidinyl)-*N*-[5-(aminocarbonyl)-2-methoxyphenyl]-1,3-thiazole-4-carboxamide; *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(2-chlorophenyl)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide; and *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(3,4-dimethylphenoxy)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide.

The above-mentioned compounds were synthesised by Reaction Scheme 2 below:

Reaction Scheme 2



5

4-Carbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (2)

Isonipecotamide **(1)** (28.8 g, 0.22 mol) was suspended in chloroform (288 mL). To this was added 4-(dimethylamino)pyridine (DMAP) (23 mg, catalytic) followed by dropwise addition of a solution of BOC-anhydride (56 g, 0.26 mol, 1.14 equiv.) in chloroform (57 mL). The solution was stirred at room temperature for 1 h and then partitioned between chloroform and 10% citric acid solution. The organic phase was washed with citric acid solution and back extracted with chloroform. The combined organic extracts were washed with water, 10% brine and dried ($MgSO_4$). Filtration followed by evaporation of the filtrate gave the crude product as a pink solid. Crystallisation from ethyl acetate/hexane gave the title compound **(2)** as a colourless solid in 4 crops (45.5 g, 0.20 mol, 89%), m.p. 159-161°C (lit. 154-156°C).

4-Thiocarbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (3)

4-Carbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (2) (45.4 g, 0.199 mol), Lawesson's reagent (40.2 g, 0.099 mol, 0.5 equiv), 1,2-dimethoxyethane (DME) (500 mL) and chloroform (200 mL) were combined and stirred at room temperature. The course of the reaction was followed by tlc analysis (30% ethyl acetate/hexane) and on completion the reaction mixture was evaporated to dryness (glassy solid). The solid was dissolved in ethyl acetate and washed with half saturated potassium carbonate solution, dried ($MgSO_4$), filtered and concentrated to yield the title compound as a colourless solid. The crude product was crystallised from ethyl acetate and hexane to give the title compound **(3)** (35 g, 0.14 mol, 72%).

4-(4-Ethoxycarbonyl-thiazol-2-yl)-piperidine-carboxylic acid *tert*-butyl ester (4)

4-Thiocarbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester **(3)** (25 g, 102 mmol) was dissolved in anhydrous *N,N*-dimethylformamide (DMF) (125 mL) and cooled to 0°C in an ice-bath. A solution of ethyl bromopyruvate (22.2 g, 14.3 mL, 114 mmol, 1.1 equiv) in anhydrous DMF (125 mL) was added dropwise with stirring. The reaction mixture was allowed to warm slowly to room temperature and stirred overnight. Triethylamine (25 mL)

was added dropwise with stirring at the rate of 1 mL/g of thioamide used. The DMF was removed *in vacuo* keeping the temperature below 60°C. The resulting residue was partitioned between ethyl acetate (75 mL) and brine (100 mL). Sufficient water was added to ensure complete dissolution of the precipitated salts in the aqueous phase. The aqueous phase was extracted twice with ethyl acetate and the combined organic extracts washed successively with brine (x2), water (x2) and brine (x2). The organic phase was simultaneously dried with $MgSO_4$ and decolourised with finely divided charcoal. The mixture was filtered through Celite and concentrated *in vacuo* to give a yellow oil. Trituration with hexane yielded a yellow solid. This was diluted with an excess of hexane and cooled overnight to allow complete crystallisation of product. The product was collected by filtration, washed with hexane and dried *in vacuo* at room temperature. Recrystallisation from IPA/water gave the title compound **(4)** (28.33 g, 83 mmol, 82%).

2-Piperidine-4-yl-thiazole-4-carboxylic acid ethyl ester (5)

To a solution of 4-(4-ethoxycarbonyl-thiazol-2-yl)-piperidine-carboxylic acid *tert*-butyl ester **(4)** (5 g, 14.7 mmol) in dichloromethane (20 mL) at 0°C was added neat trifluoroacetic acid (TFA) (17 mL, 221 mmol, 15 equivalents) dropwise with stirring, under an inert atmosphere. On completion of addition the reaction mixture was allowed to warm to room temperature and stirring continued until deprotection complete (typically 3 hours, monitored by tlc, 1:1 hexane/ethyl acetate). On completion of reaction the mixture was concentrated *in vacuo* to remove TFA. Toluene (dioxan for **(6f)**) was then added and re-concentrated to further remove TFA - this was repeated 2-3 times to ensure maximum removal of TFA. The product was further dried *in vacuo* overnight to remove the last traces of TFA. The TFA salt of the free amine was dissolved in dichloromethane (10 mL), cooled to 0°C in an ice bath and treated with triethylamine (6.15 mL, 3 equiv). It was assumed a quantitative conversion of BOC-protected **(4)** to free amine **(5)**.

Compounds (6a-e)

To a solution of 2-piperidine-4-yl-thiazole-4-carboxylic acid ethyl ester **(5)** (14.7 mmol) in dichloromethane (10 mL) at 0°C was added acetonitrile (40 mL). To this solution was

sequentially added the acid to be reacted (R1COOH – see Table 2) (14.7mmol, 1 equiv.), *N,N,N',N'*-tetramethyl-O-(*1H*-benzotriazole-1-yl) uronium hexafluorophosphate (HBTU) (14.7mmol, 5.57g, 1 equiv.), and *N,N*-diisopropylethylamine (DIPEA) (7.7 mL, 3 equiv.). The reaction mixture was stirred at room temperature for 48 h to allow for completion of reaction. After this time the reaction mixture was concentrated *in vacuo* to remove the solvent and the residue was suspended in dichloromethane (80 mL) and washed with brine (2 x 50 mL), water (50 mL), 10% citric acid (50 mL), brine, saturated sodium bicarbonate solution (50 mL) and finally brine. The organic layer was dried over $MgSO_4$ and treated with decolourising charcoal, filtered and concentrated *in vacuo*.

Table 2

id	$R1CO_2H$	yield
6a	2-chlorophenylacetic acid	not purified
6b	3,4-dimethylphenoxyacetic acid	not purified
6c	1-benzofuran-2-carboxylic acid	65% (after chromatography)
6d	3-phenylpropynic acid	not purified
6e	2-(allylthio)nicotinic acid	not purified
6f	4,7-dimethylpyrazolo[5,1-c][1,2,4]triazine-3-carboxylic acid	not purified

Compounds (7a-e)

Compound **(6a-e)** (13mmol) was dissolved in THF (35 mL) and water (23 mL) and cooled to 0°C. A solution of sodium hydroxide (1.04g, 26mmol, 2 equiv.) in water (20 mL) was added dropwise with stirring. The reaction was monitored by tlc analysis and when complete (typically 2 h) the reaction mixture was diluted with brine (30 mL) and washed with ether (100 mL). The reaction mixture was acidified using 20% citric acid solution. The acidic mixture was then extracted with a suitable organic solvent (dichloromethane or ethyl acetate) and when fully extracted the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield essentially pure product.

Table 3

id	extraction solvent	yield
7a	ethyl acetate	58% (over two steps)
7b	ethyl acetate	61% (over two steps)
7c	ethyl acetate	80%
7d	dichloromethane	41% (over two steps)
7e	ethyl acetate	54% (over two steps)
7f	ethyl acetate	53% (over two steps)*

*product was isolated by repeated crystallisation from ethyl acetate

Compounds (8a-e)

Compound (**7a-e**) was dissolved in anhydrous DMF (0.58 M solution). 3-Amino-4-methoxybenzamide was dissolved in 10% DIPEA and anhydrous DMF (0.58 M solution). HBTU was dissolved in anhydrous DMF (0.64 M solution). The amine solution (0.3 ml, 0.175 mmol) was dispensed into an individual well in a 2.2 mL deep well plate using a Packard MPII robot. An Eppendorf multi-dispenser was used to dispense the acid solution (0.3 mL, 0.175 mmol, 1 equiv) and then to dispense the HBTU solution (0.3 mL, 0.19 mmol, 1.1 equiv). A further portion of DIPEA (0.05 mL) was added to the well, which was capped and shaken on an orbital shaker overnight. The reaction mixture was concentrated *in vacuo* (Genevac). The residue was dissolved in dichloromethane (1 mL) and given a sequence of aqueous washes using the MPII robot: 0.5 N HCl (0.7 mL), 10% potassium carbonate solution (0.7 mL) then water (0.7 mL). Finally the dichloromethane extract (0.7 mL) containing the product was concentrated and dried (Genevac) to constant mass.

Table 4

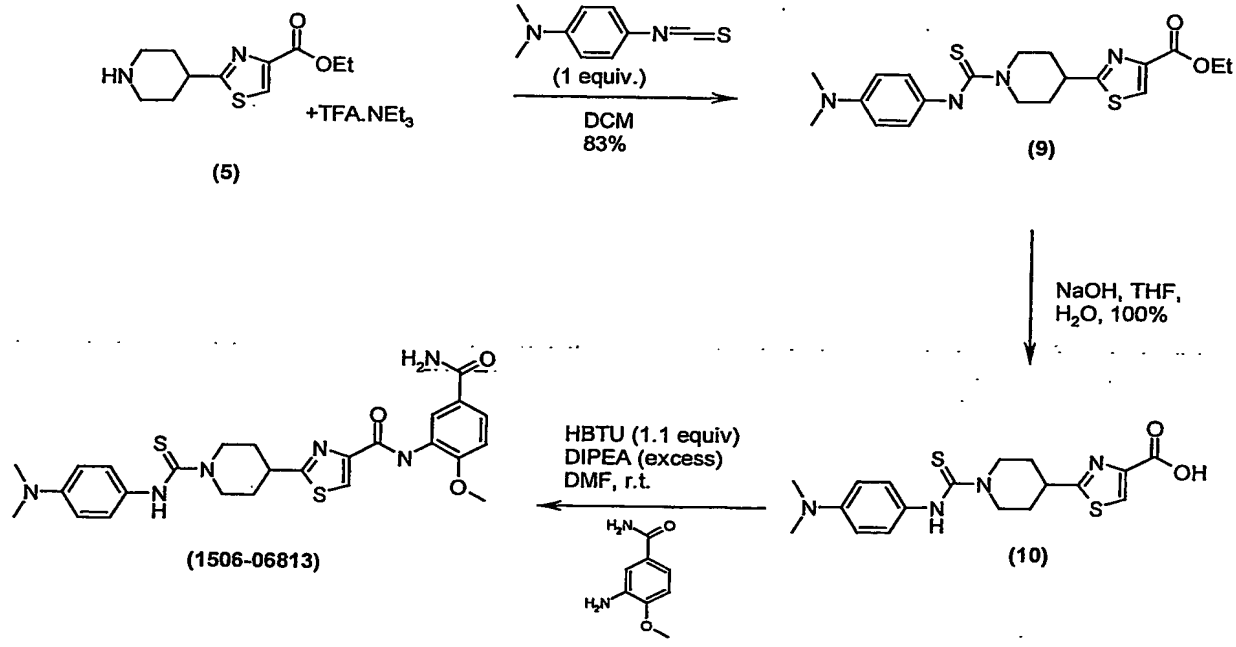
id	RRcode	DAD (254 nm)	ES+
8a	1506-03737	100%	513
8b	1506-03914	97%	523
8c	1506-01284	88%	505
8d	1506-01461	90%	489
8e	1506-02331	89%	538
8f	1506-00581	86%	535

Example 7

Preparation of *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({[4-(dimethylamino)phenyl]amino}carbonothioyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({[4-(dimethylamino)phenyl]amino}carbonothioyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide was prepared by the synthetic route set out in Reaction Scheme 3 below.

Reaction Scheme 3



2-[1-(4-Dimethylamino-phenylthiocarbamoyl)-piperidine-4-yl]-thiazole-4-carboxylic acid ethyl ester (9)

To a solution of 2-piperidine-4-yl-thiazole-4-carboxylic acid ethyl ester **(5)** (14.7 mmol) in dichloromethane (10 mL) at 0°C was added dichloromethane (80 mL). To this was added 4-(dimethylamino)phenylisothiocyanate (14.7mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 48 h to allow for completion of reaction. After this time the reaction mixture was diluted with dichloromethane (100 mL) and washed with water (2 x 100 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the thiourea in 83% yield following chromatography.

2-[1-(4-Dimethylamino-phenylthiocarbamoyl)-piperidine-4-yl]-thiazole-4-carboxylic acid (10)

2-[1-(4-Dimethylamino-phenylthiocarbamoyl)-piperidine-4-yl]-thiazole-4-carboxylic acid ethyl ester **(9)** (13 mmol) was dissolved in THF (35 mL) and water (23 mL) and cooled to 0°C. A solution of sodium hydroxide (1.04g, 26 mmol, 2 equiv.) in water (20 mL) was added dropwise with stirring. The mixture was stirred for 2 h at r.t. The mixture was diluted with brine (30 mL) and washed with ether (100 mL). The reaction mixture was acidified using 20% citric acid solution. The acidic mixture was extracted with ethyl acetate and when fully extracted the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound **(10)** in quantitative yield.

***N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({[4-(dimethylamino)phenyl]amino}carbonothioyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide**

2-[1-(4-Dimethylamino-phenylthiocarbamoyl)-piperidine-4-yl]-thiazole-4-carboxylic acid **(10)** was dissolved in anhydrous DMF (0.58 M solution). 3-Amino-4-methoxybenzamide was dissolved in 10% DIPEA and anhydrous DMF (0.58 M solution). HBTU was dissolved in anhydrous DMF (0.64 M solution). The amine solution (0.3 ml, 0.175 mmol) was dispensed into an individual well in a 2.2 mL deep well plate using a Packard MPII

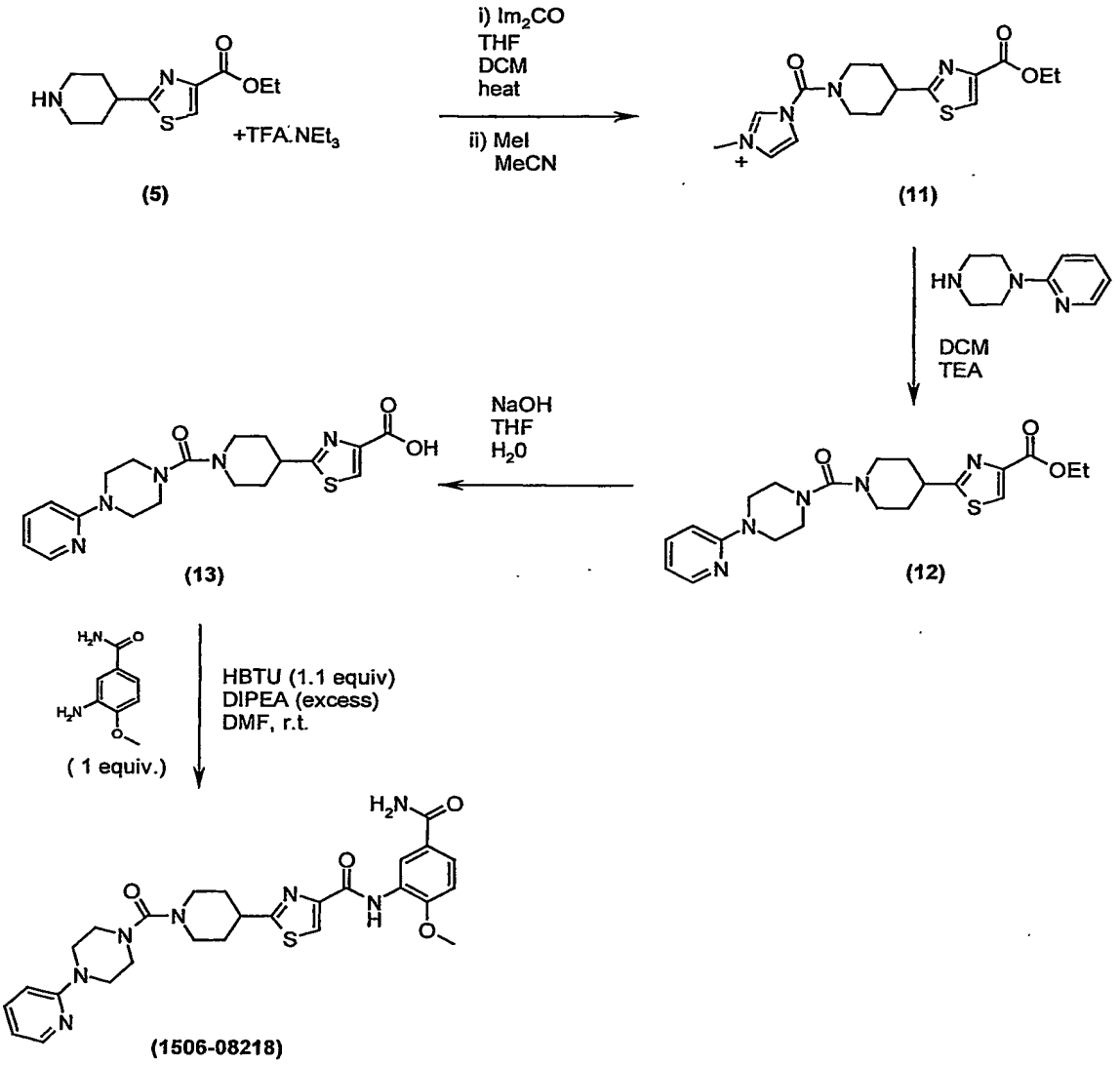
robot. An Eppendorf multi-dispenser was used to dispense the acid solution (0.3 mL, 0.175 mmol, 1 equiv) and then to dispense the HBTU solution (0.3 mL, 0.19 mmol, 1.1 equiv). A further portion of DIPEA (0.05 mL) was added to the well, which was capped and shaken on an orbital shaker overnight. The reaction mixture was concentrated *in vacuo* (Genevac). The residue was dissolved in dichloromethane (1 mL) and given a sequence of aqueous washes using the MPII robot: 0.5 N HCl (0.7 mL), 10% potassium carbonate solution (0.7 mL) then water (0.7 mL). Finally the dichloromethane extract (0.7 mL) containing the product was concentrated and dried (Genevac) to constant mass to give *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({[4-(dimethylamino)phenyl]amino}carbonothioyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide (DAD 75% (254nm), ES+ 539).

Example 8

Preparation of *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide was prepared by the synthetic route set out in Reaction Scheme 4 below.

Reaction Scheme 4



3-[4-(4-Ethoxycarbonyl-thiazol-2-yl)-piperidine-1-carbonyl]-1-methyl-*3H*-imidazol-1-ium (11)

A solution of 2-piperdine-4-yl-thiazole-4-carboxylic acid ethyl ester (**5**) (14.7 mmol) in dichloromethane (15 mL) was added dropwise to a suspension of carbonyldiimidazole in tetrahydrofuran (15 mL). The mixture was heated at reflux overnight then cooled to room temperature. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (80 mL), washed with water and dried over $MgSO_4$ and concentrated *in*

vacuo. The residue was dissolved in acetontrile and methyl iodide added (59 mmol). The mixture was stirred overnight and concentrated to give the title compound which was used without purification.

2-[1-(4-Pyridine-2-yl-piperazine-1-carbonyl)-piperidin-4-yl]-thiazole-4-carboxylic acid ethyl ester (12)

3-[4-(4-Ethoxycarbonyl-thiazol-2-yl)-piperidine-1-carbonyl]-1-methyl-*3H*-imidazol-1-ium **(11)** was taken up in dichloromethane (75 mL) and 1-(2-pyridyl)piperazine (14.7 mmol, 1 equiv.) and triethylamine (14.7 mmol, 1 equiv.) added. The mixture was stirred overnight and diluted with dichloromethane. The mixture was washed with water and brine, dried and concentrated *in vacuo* to yield the title compound which was used without purification.

2-[1-(4-Pyridine-2-yl-piperazine-1-carbonyl)-piperidin-4-yl]-thiazole-4-carboxylic acid ethyl ester (13)

The ethyl ester **(12)** was taken up in tetrahydrofuran (40 mL) / water (20 mL) and sodium hydroxide (29.4 mmol) in water (20 mL) added. The mixture was stirred for 2 h at room temperature. The mixture was then extracted with ether and the aqueous phase acidified with 10% citric acid solution. The aqueous phase was extracted with ethyl acetate and the combined extracts washed with brine, dried and concentrated *in vacuo*. Precipitated product remaining in the aqueous layer was filtered, dried and added to the residue. The title compound **(13)** was obtained as a colourless solid [total yield 59% (3 steps)].

***N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide**

2-[1-(4-Pyridine-2-yl-piperazine-1-carbonyl)-piperidin-4-yl]-thiazole-4-carboxylic acid ethyl ester **(13)** was dissolved in anhydrous DMF (0.58 M solution). 3-Amino-4-methoxybenzamide was dissolved in 10% DIPEA and anhydrous DMF (0.58 M solution). HBTU was dissolved in anhydrous DMF (0.64 M solution). The amine solution (0.3 ml, 0.175 mmol) was dispensed into an individual well in a 2.2 mL deep well plate using a

Packard MPII robot. An Eppendorf multi-dispenser was used to dispense the acid solution (0.3 mL, 0.175 mmol, 1 equiv) and then to dispense the HBTU solution (0.3 mL, 0.19 mmol, 1.1 equiv). A further portion of DIPEA (0.05 mL) was added to the well, which was capped and shaken on an orbital shaker overnight. The reaction mixture was concentrated *in vacuo* (Genevac). The residue was dissolved in DCM (1 mL) and given a sequence of aqueous washes using the MPII robot: 0.5 N HCl (0.7 mL), 10% potassium carbonate solution (0.7 mL) then water (0.7 mL). Finally the DCM extract (0.7 mL) containing the product was concentrated and dried (Genevac) to constant mass to give *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide (DAD 100% (254nm), ES+ 550).

Activity Assays

Activities of compounds of the invention were tested using the following assays. The results of the assays are set out in table 5 below. For some compounds the assays were repeated to give the multiple results shown in the table.

Initially the compounds were assayed for inhibition of VEGF in a medium throughput ELISA assay before detailed assessment in the HUVEC and VEGF binding assays in examples in 9 and 10. The data from this initial assessment is presented in table 5 in the column labelled "Inhibition %".

Example 9 - Human umbilical vein endothelial cells (HUVEC) proliferation assay

The HUVEC assay measures the potency of test substances to inhibit *in vitro* proliferation of human umbilical vein endothelial cells (HUVEC) when co-stimulated with recombinant human vascular endothelial growth factor (rhVEGF).

HUVEC are grown under defined conditions (EGM-2 medium, 37°C, 5 % CO_2 and 95 % humidity). They are seeded into 48-well plates using EBM medium with only 1 % serum and incubated for 24 h. This is to ensure that cells are not stimulated before treatment with VEGF and test compound.

Test compounds are diluted in medium to concentrations between 0.05 and 50 µM and dosed together with $VEGF_{165}$ at 12 ng/ml. This VEGF concentration was determined in a VEGF-dose-response curve to be just sub-optimal for maximum cell proliferation. Cells are incubated for 48 h at above conditions and viable cell density is measured using a tetrazolium compound (MTS). Viable cells reduce MTS into a soluble formazan product, which has an absorbance maximum at 490 nm. The absorbance is directly proportional to cell density.

Control values are: EBM + 1 % serum (no VEGF) ⇒ Minimum or Blank
EBM + 1 % serum (12 ng/ml) ⇒ Maximum

Example 10 - VEGF-binding ELISA

The potency of test substances as a VEGF-neutralising moiety is measured in an ELISA format. This assay measures the solution-phase interaction between $rhVEGF_{165}$-biotin and test sample. Unbound $VEGF_{165}$-biotin is then immobilised on a solid-phase anti-hVEGF antibody (R&D systems MAB293). The biotin signal is detected with streptavidin-alkaline phosphatase, which gives a colorimetric signal when incubated with p-nitrophenyl phosphate. Plates are read in a spectrophotometer at 405 nm.

Any test compound that binds to VEGF165-biotin and prevents it from binding to the antibody will lower the color signal and be recognized as a "hit". Hits were defined as compounds that show > 60 % inhibition.

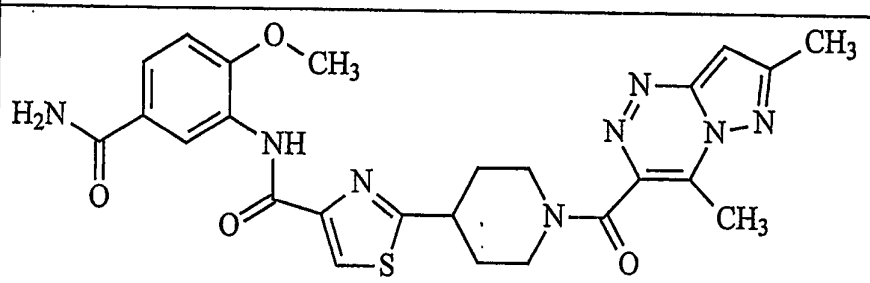
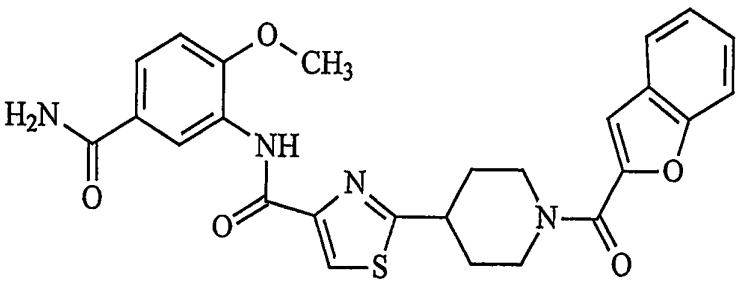
Control values are: VEGF165-biotin + assay buffer ⇒ 0 % inhibition
Soluble VEGF receptor (sflt @ 4 nM) ⇒ 70 % inhibition

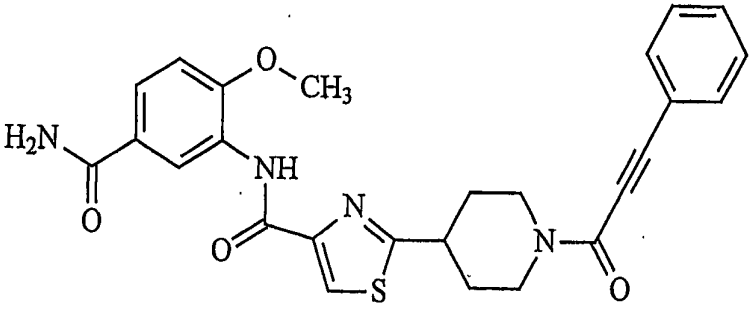
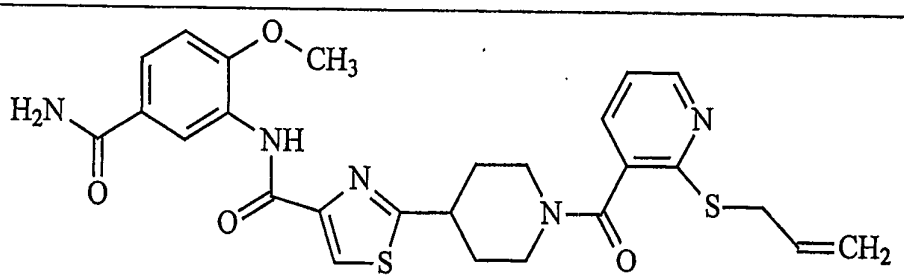
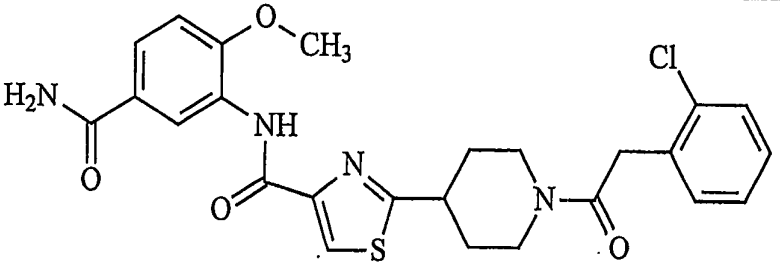
The primary screening of all library compounds was done at a compound concentration of 50 µM, followed by measuring dose-response effects of "hits" between 0.05 and 500 µM for the calculation of IC_{50} values.

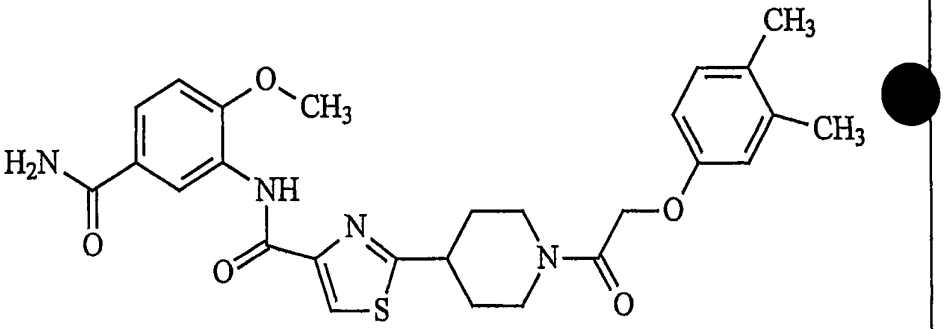
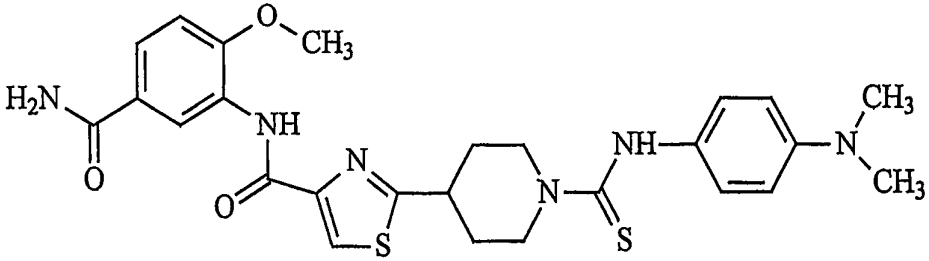
The compounds were dissolved in DMSO and it was shown that the solvent has no effect on the assay at this concentration.

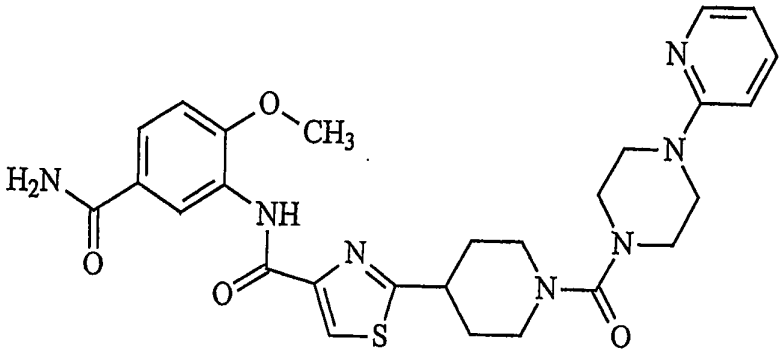
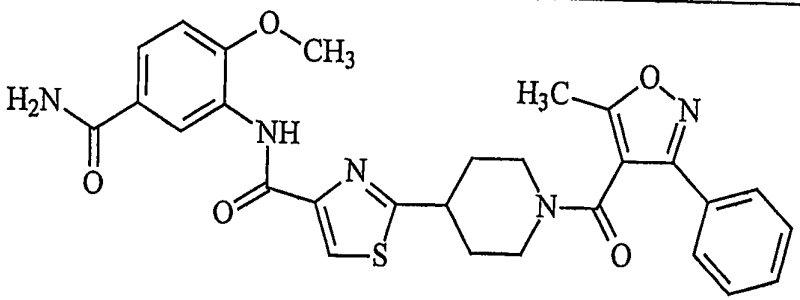
Table 5

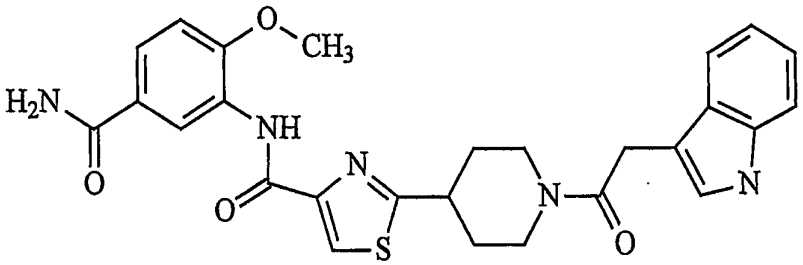
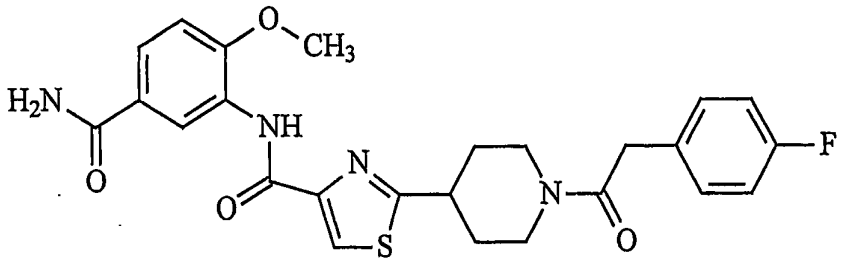
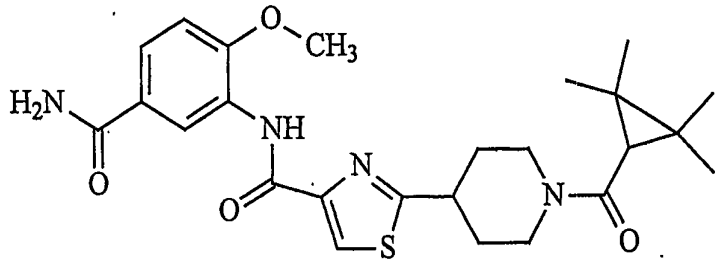
Activities of compounds of the invention

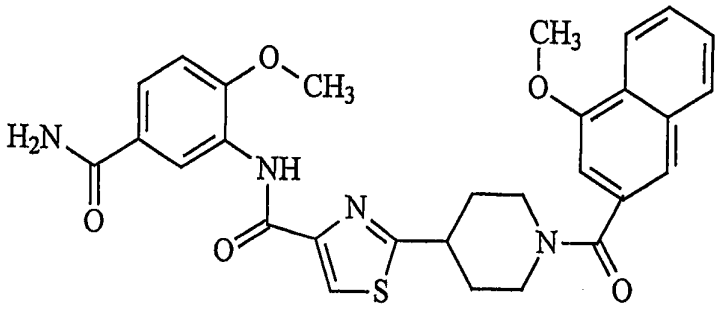
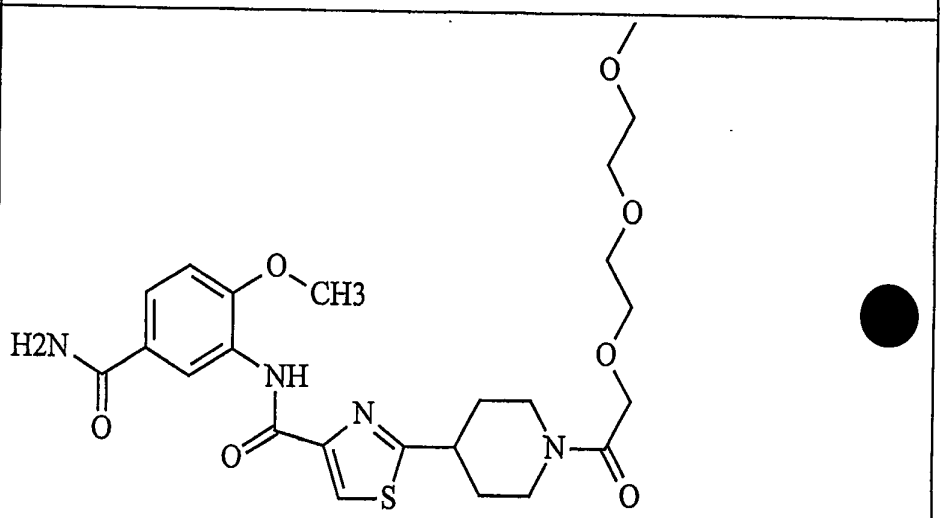
Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-00581	M2025-0001	88	4.4 5.0	30 31	
1506-01284	M2025-0002	85	11.0 13.5	10.1 12.6	

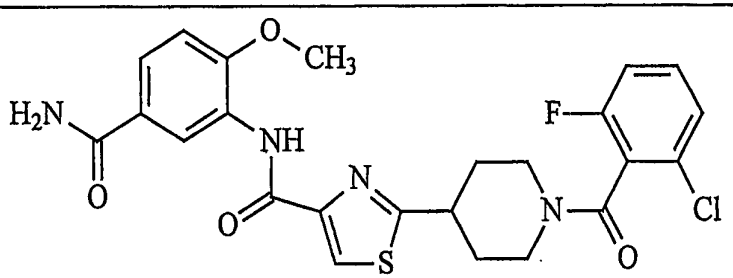
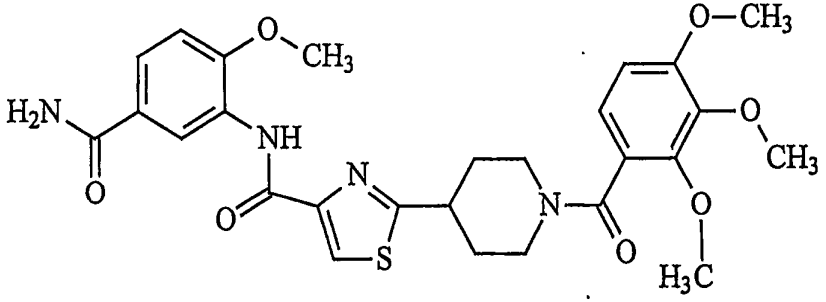
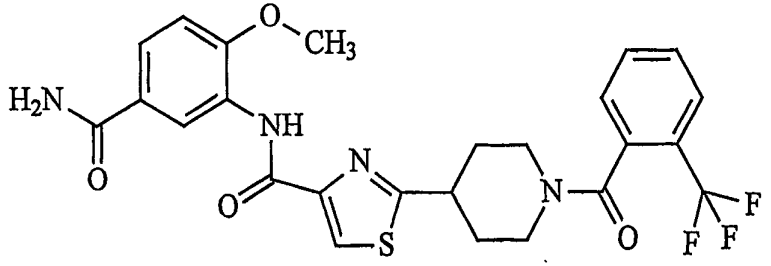
Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-01461	M2025-0003	88 75 83	4	11	
1506-02331	M2025-0004	43 73 79	6.5	22.8	
1506-03737	M2025-0005	60 70 74	214 8	9	

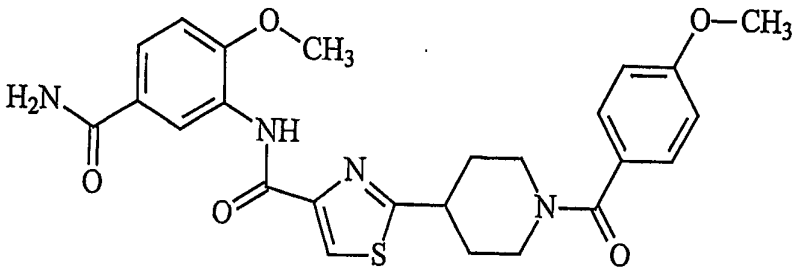
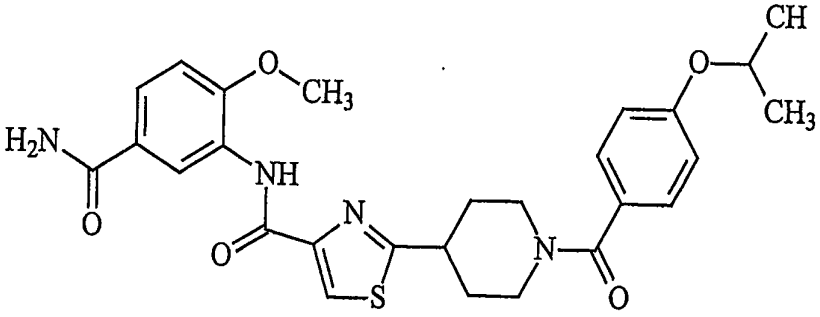
Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-03914	M2025-0006	77 70 81	4.5	17	
1506-06813	M2025-0007	88	7.3 1.5	9.7 8.2	

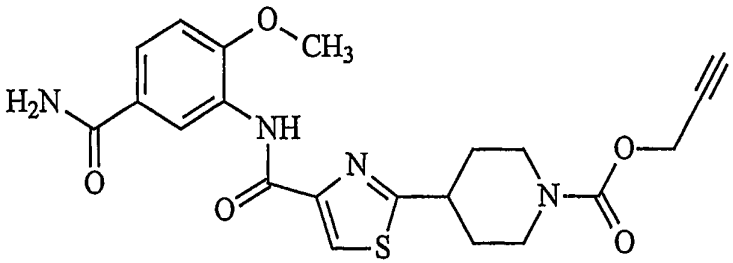
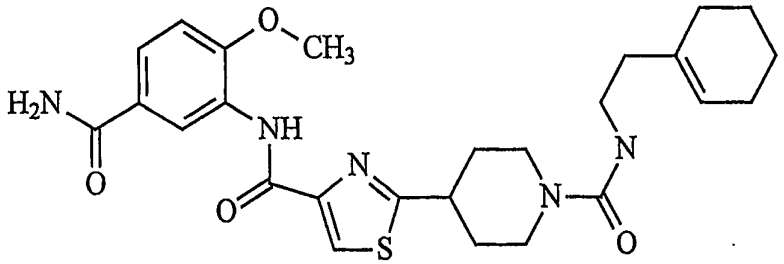
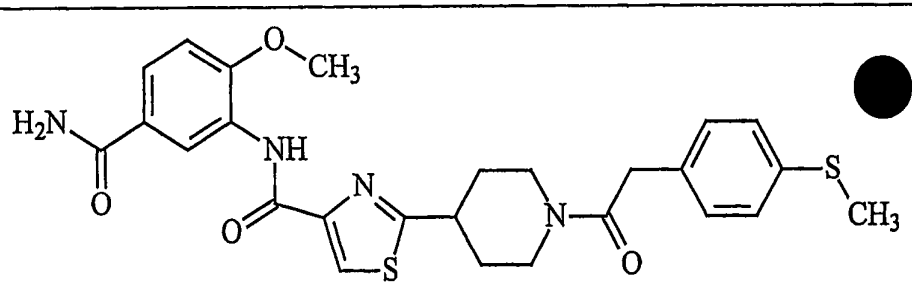
Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-08218	M2025-00008	52 60 67	14.8	15.4	
1506-00404		72 -49 -35	153	10.4	

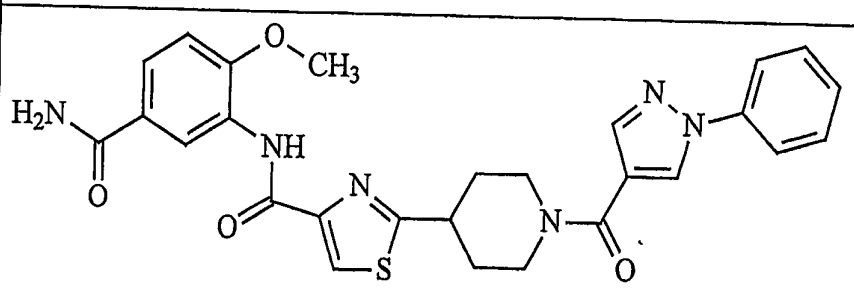
Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-00935		65 51 31	29		
1506-01112		11 17 55	16.7	26	
1506-01638		89	71 >100	5.4 6.0	

Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-01810		-43 -10 -14	136	5.6	
1506-02159		46 -20 -83	128		

Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-03039		63 -13 -67	105	4.2	
1506-03211		64 -24 -80	132		
1506-03388		93 87 90	6.6	23	

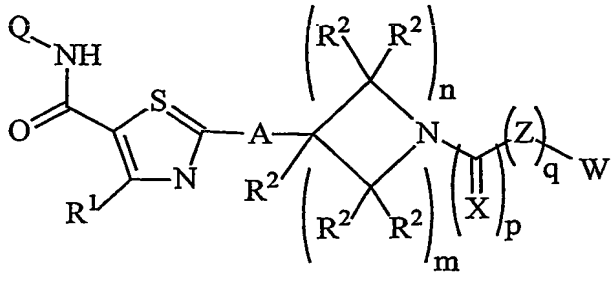
Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-03560		42 88 85	3.6	16.4	
1506-04091		71 56 19	16.0 15.5		

Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-07095		61 -37 -63	173		
1506-07554		84 -15 -83	142	35	
1506-08674		64 84 36	11.0		

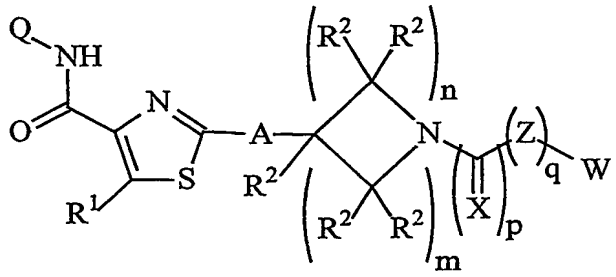
Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-08772		91	54 126	25	

CLAIMS

1. A compound of formula (I) or formula (II):



(I)



(II)

wherein:

Q is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, amino, alkylamino, dialkylamino, carboxyl, carboxylalkyl, esterified carboxyl, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy, or heterocyclic group;

A is a single bond or alkylene;

X is O or S;

Z is O, S or NR^3;

p is 0 or 1

q is 0 or 1;

n is an integer from 0 to 10;

m is an integer from 0 to 10;

W is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, amino, alkylamino, dialkylamino, carboxyl, carboxylalkyl,

esterified carboxyl, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy, or heterocyclic group;

R^1 is H or alkyl;

R^2 is independently H or alkyl; and

R^3 is H or alkyl;

or a pharmaceutically acceptable derivative thereof.

2. A compound of claim 1 selected from:

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(4,7-dimethylpyrazolo[5,1-*c*][1,2,4]triazin-3-yl)carbonyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-(1-benzofuran-2-ylcarbonyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-(3-phenyl-2-propynoyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide;

2-(1-{[2-(allylsulfanyl)-3-pyridinyl]carbonyl}-4-piperidinyl)-*N*-[5-(aminocarbonyl)-2-methoxyphenyl]-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(2-chlorophenyl)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(3,4-dimethylphenoxy)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({[4-(dimethylamino)phenyl]amino}carbonothioyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide;

or

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide.

3. The compound of any one of claims 1 to 2 for use in therapy or diagnosis.

4. Use of a compound of any one of claims 1 to 2 for use in the manufacture of a medicament for treating a VEGF-mediated disorder.

5. The use of claim 4, wherein the condition is endometriosis or cancer.

6. A method of treating a VEGF-mediated disorder comprising administrating to a patient in need of such treatment an effective dose of a compound of any one of claims 1-2.

7. A pharmaceutical composition comprising a compound of any one of claims 1-2 in combination with a pharmaceutically acceptable diluent.